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Guest editorial

Feline coronavirus – that enigmatic little critter

At the recent Second International Feline Coronavirus/Feline Infectious Peritonitis Symposium (SIFFS Scotland 2002), Dr. Jim Richards aptly described feline coronavirus (FCoV) as an "enigmatic little critter!" Feline infectious peritonitis (FIP) was first described in 1964 (Holzworth, 1963) and nearly 40 years on, very little is known about this complicated disease, there is no single diagnostic test, no treatment and only one vaccine (which is not at present available in the UK). In fact, the pathogenesis of FIP is hardly understood at all and every advance of science seems to make it harder, rather than easier, to understand. For diagnosis, clinicians use a panel of tests including FCoV serology, albumin to globulin ratio, haematology, cytology of effusion and measurement of acute phase proteins, especially α1-acid glycoprotein (AGP). There are many publications about the virtues and limitations of these tests in cats with FIP, but, as far as I know, Dr. Giordano's paper, published in this issue of *The Veterinary Journal*, is the first time that workers have looked at the relevant differences in these parameters in the cats who get FIP and their in-contact cats who remain healthy (Giordano et al., 2004).

Physically (if not emotionally) it is easy to take laboratory grown viruses and inoculate them into groups of specific pathogen free cats and then publish the results. What Professor Paltrinieri's group does is far more difficult – following naturally infected cats – but their results are much more trustworthy and more likely to represent what really happens in the field. Dr. Giordano and her colleagues address the down-to-earth questions: "How do I diagnose this disease in the living cat?" and "How do I distinguish the FCoV infected cat from the cat with FIP?" Like Duthie et al. (1997), they found that cats with FIP were likely to have higher AGP concentrations, and that haptoglobin levels were not predictive. But, unlike Duthie, they examined a group of FCoV-exposed cats and asked what was the difference between them and the cats with FIP? This is a question which constantly arises in real life, and Dr. Giordano is the first to present an answer: she found that there was a massive increase in serum amyloid A (SAA) compared with FCoV exposed cats. It would appear that SAA should be added to the panel of tests performed on the suspect FIP case.

What is very interesting and unique about this study is the following of four FCoV exposed cats over 83 days. It was extraordinary that when FIP occurred in one cat, the in-contact cats' acute phase proteins fluctuated. The significance is that these fluctuations did not appear with FCoV infection, *but with the development of FIP in one of the cats*. If this is truly the case, it would imply that the mutated, pathogenic form, FIPV, had spread to the other cats. Present belief is that for cats to develop FIP, a mutation (more accurately – a deletion) must occur in the viral genome of non-pathogenic FCoVs (so called enteric coronaviruses) which allows the virus to replicate in macrophages (Vennema et al., 1998). The current theory is that the mutated virus cannot transmit to other cats, although this theory was challenged at SIFFS as delegates had experienced households where many cats had developed FIP, implying that virulent virus had spread (Addie et al., in press).

The mechanism by which cats do not get FIP is not understood at present. In Giordano's paper, four surviving cats had a transient rise in SAA and the authors ask the interesting question as to whether this increase and the decrease in AGP seen in these cats had some protective role? Although the biological function of AGP is not completely known, it is a natural anti-inflammatory and immunomodulatory agent. Its effects in relation to FIP development could be protective or damaging. Examples of AGP's protective properties are: (1) it has anti-complement activity (Fournier et al., 2000), and FIP is an immune-mediated disease such that cats which are decomplemented do not develop FIP and (2) AGP's immunomodulatory and anti-neutrophil activity: in FIP chemokines are released which attract neutrophils – one of the cell types in FIP pyogranulomas.

On the other hand, AGP may exacerbate the effects of FIP by maintaining capillary permeability in animals with shock (Fournier et al., 2000) and clearly cats with effusive FIP have very permeable capillaries. Moreover, AGP from humans with cancer suppressed the augmentation of natural killer (NK) cell activity by interferon α or γ (Aso et al., 1999); suppression of NK cell activity could allow the virus to replicate more.

The immunomodulatory function of AGP is affected by its carbohydrate composition (Aso et al., 1999; Fournier et al., 2000). The sialyl Lewis X form of AGP

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is induced during inflammation and ameliorates both complement and neutrophil-mediated injuries while the non-sialyl Lewis X form does not (Fournier et al., 2000). Moreover, sialyl Lewis X is the ligand for the cell adhesion molecules involved in adhesion of monocytes to endothelial cells (Fournier et al., 2000), and one of the earliest stages of the pathogenesis of FIP is the adhesion of FCoV-infected monocytes to the endothelium in FIP vasculitis. Is it possible that development of FIP has got little to do with the virus after all and everything to do with the AGP response of the cat?

Sequential testing of symptomatic cats is a large gap in the area of FIP diagnosis and treatment and needs to be filled. I have followed one cat with FIP over the time of treatment until death and I found that AGP and globulin levels correlated well with response to treatment and improving or worsening clinical signs, whereas repeatedly measuring FCoV antibody titre was unhelpful. AGP and globulin levels fell when the cat responded well to treatment and rose when the cat relapsed, but the FCoV antibody titre remained high. I hope that Professor Paltrinieri's group will expand this particular area of research in future as it would be especially good to be able to correlate clinical pathology results with clinical response to treatment. Establishment of objective markers for clinical improvement would also make evaluation of potential treatments easier.

Dr. Giordano's paper is interesting, and it points the way to future research. Nevertheless, her results must be confirmed on larger numbers of cats, SAA levels should be studied in the many differential diagnoses of FIP and, of course, we need to understand whether and how acute phase proteins enable FCoV exposed cats to recover from the infection in order to ascertain if therein lies a potential for FIP treatment – and control of that critter.

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References

Addie, D.D., Paltrinieri, S., Pedersen, N.C., in press. Recommendations from workshops of the second international feline coronavirus/feline infectious peritonitis symposium. Journal of Feline Medicine and Surgery.

Aso, H., Tamura, K., Rose, M.T., Tomioka, Y., Mizugaki, M., Ishida, N., 1999. Effect of α1-acidic glycoprotein in the ascitic fluid of cancer patients on human NK cells: selective suppression of interferon-induced NK activation. Inflammation 23, 117–129.

Duthie, S., Eckersall, P.D., Addie, D.D., Lawrence, C.E., Jarrett, O., 1997. Value of α1-acid glycoprotein in the diagnosis of feline infectious peritonitis. Veterinary Record 141, 299–303.

Fournier, T., Medjoubi, N.N., Porquet, D., 2000. α-1-acid glycoprotein. Biochimica et Biophysica Acta 1482, 157–171.

Giordano, A., Spagnolo, V., Colombo, A., Paltrinieri, S., 2004. Changes in some acute phase protein and immunoglobulin concentrations in cats affected by feline infectious peritonitis (FIP) or exposed to feline coronavirus infection. The Veterinary Journal, this issue. X-ref:doi:10.1016/S1090-0233(03)00055-8.

Holzworth, J., 1963. Some important disorders of cats. Cornell Veterinarian 53, 157–160.

SIFFS website: www.felinecoronavirus.com.

Vennema, H., Poland, A., Foley, J., Pedersen, N.C., 1998. Feline infectious peritonitis viruses arise by mutation from endemic feline enteric coronaviruses. Virology 243, 150–157.